ANNALS OF SURGERY
Vol. 230, No. 3, 322–330

Is Prophylactic Gastrojejunostomy Indicated for Unresectable Periampullary Cancer?

A Prospective Randomized Trial

Keith D. Lillemoe, MD, John L. Cameron, MD, Jeffrey M. Hardacre, MD, Taylor A. Sohn, MD, Patricia K. Sauter, RN, ACNP, JoAnn Coleman, RN, CRNP, Henry A. Pitt, MD, and Charles J. Yeo, MD

From the Department of Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Objective

This prospective, randomized, single-institution trial was designed to evaluate the role of prophylactic gastrojejunostomy in patients found at exploratory laparotomy to have unresectable periampullary carcinoma.

Summary Background Data

Between 25% and 75% of patients with periampullary cancer who undergo exploratory surgery with intent to perform a pancreaticoduodenectomy are found to have unresectable disease. Most will undergo a biliary–enteric bypass. Whether or not to perform a prophylactic gastrojejunostomy remains unresolved. Retrospective reviews of surgical series and prospective randomized trials of endoscopic palliation have demonstrated that late gastric outlet obstruction, requiring a gastrojejunostomy, develops in 10% to 20% of patients with unresectable periampullary cancer.

Methods

Between May 1994 and October 1998, 194 patients with a periampullary malignancy underwent exploratory surgery with the purpose of performing a pancreaticoduodenectomy and were found to have unresectable disease. On the basis of preoperative symptoms, radiologic studies, or surgical findings, the surgeon determined that gastric outlet obstruction was a significant risk in 107 and performed a gastrojejunostomy. The remaining 87 patients were thought by the surgeon not to be at significant risk for duodenal obstruction and were randomized to receive either a prophylactic retrocolic gastrojejunostomy or no gastrojejunostomy. Short- and long-term outcomes were determined in all patients.

Results

Of the 87 patients randomized, 44 patients underwent a retrocolic gastrojejunostomy and 43 did not undergo a gastric bypass. The two groups were similar with respect to age, gender, procedure performed (excluding gastrojejunostomy), and surgical findings. There were no postoperative deaths in either group, and the postoperative morbidity rates were comparable (gastrojejunostomy 32%, no gastrojejunostomy 33%). The postoperative length of stay was 8.5 ± 0.5 days for the gastrojejunostomy group and 8.0 ± 0.5 days for the no gastrojejunostomy group. Mean survival among those who received a prophylactic gastrojejunostomy was 8.3 months, and during that interval gastric outlet obstruction developed in none of the 44 patients. Mean survival among those who did not have a prophylactic gastrojejunostomy was 8.3 months. In 8 of those 43 patients (19%), late gastric outlet obstruction developed, requiring therapeutic intervention (gastrojejunostomy 7 patients, endoscopic duodenal stent 1 patient; $p < 0.01$). The median time between initial exploration and therapeutic intervention was 2 months.

Conclusion

The results from this prospective, randomized trial demonstrate that prophylactic gastrojejunostomy significantly decreases the incidence of late gastric outlet obstruction. The performance of a prophylactic retrocolic gastrojejunostomy at the initial surgical procedure does not increase the incidence of postoperative complications or extend the length of stay. A retrocolic gastrojejunostomy should be performed routinely when a patient is undergoing surgical palliation for unresectable periampullary carcinoma.

Periampullary adenocarcinoma (carcinoma of the head of the pancreas, distal bile duct, ampulla of Vater, or duodenum) is a common cause of cancer death in the United States, with more than 30,000 deaths annually. Surgical resection by pancreaticoduodenectomy provides the only chance for cure for patients with periampullary carcinoma.

Presented at the 119th Annual Meeting of the American Surgical Association, April 15–17, 1999, Hyatt Regency Hotel, San Diego, California.
Dr. Pitt is currently with the Medical College of Wisconsin, Milwaukee, Wisconsin.
Correspondence: Keith D. Lillemoe, MD, The Johns Hopkins Hospital, Dept. of Surgery, Blalock 679, 600 N. Wolfe St., Baltimore, MD 21287-4603.
Accepted for publication April 1999.

Therefore, an aggressive approach to the surgical management of this disease is advocated in most centers. However, 25% to 75% of patients with periampullary tumors who undergo exploratory surgery with intent to perform a pancreaticoduodenectomy are found to have unresectable disease.[1–4] Therefore, at the time of laparotomy, the surgeon must focus on appropriate palliation of the disease. Because obstructive jaundice is the presenting symptom in most patients with periampullary carcinoma, the performance of a biliary-enteric bypass is considered routine by most surgeons. The decision as to whether to perform a gastrojejunostomy in patients without obvious gastroduodenal obstruction secondary to the tumor remains unresolved. Retrospective reviews of surgical series[5–7] and prospective randomized trials of endoscopic palliation[8–10] have demonstrated that in 10% to 20% of patients with unresectable pancreatic cancer, late gastric outlet obstruction will develop, requiring a gastrojejunostomy. Despite these data, many surgeons do not believe that routine prophylactic gastrojejunostomy should be performed. This important question has not been previously addressed in a properly constructed, prospective randomized trial. The current prospective, randomized, single-institution study was therefore designed to determine both the short- and long-term outcomes and benefits associated with prophylactic gastrojejunostomy in patients with unresectable periampullary carcinoma.

PATIENTS AND METHODS

This study was approved by the Joint Committee on Clinical Investigation of The Johns Hopkins University School of Medicine. Patients were recruited into the study before surgery on the basis of anticipation of pancreaticoduodenal resection for adenocarcinoma of the periampullary region, and appropriate informed consent was obtained. Between May 1994 and October 1998, 709 patients with a periampullary malignancy underwent exploratory surgery with the purpose of performing a pancreaticoduodenectomy. Of the 709 patients, 194 (27%) were found to have unresectable disease. On the basis of symptoms, preoperative radiologic studies, or intraoperative findings, the attending surgeon determined that gastric outlet obstruction was a significant risk in 107 patients, and therefore a gastrojejunostomy was performed. The remaining 87 patients were thought by the surgeon not to be at a significant risk for duodenal obstruction and were included in the randomization.

Surgical Technique

Patients were randomized (using a computer-generated random number pattern) during surgery after determination by the attending surgeon that pancreaticoduodenectomy was not possible due to the extent of the disease and that duodenal obstruction in the future was unlikely. Patients were randomized to receive either a retrocolic gastrojejunostomy performed to the most dependent portion of the gastric antrum, or no gastrojejunostomy. A vagotomy was not performed. Other palliative procedures including hepaticojejunostomy, cholecystectomy, and chemical splanchnicectomy[11] were performed at the discretion of the attending surgeon. Feeding jejunostomies were not routinely used. A histiologic diagnosis was obtained in all patients to confirm the diagnosis of adenocarcinoma.

Postoperative Management

All patients received a histamine H_2-receptor antagonist during their postoperative hospital stay as prophylaxis for stress and marginal ulceration. Nasogastric suction and prokinetic agents were used at the discretion of the attending surgeon. Initiation and advancement of diet and length of hospital stay were directed by the surgical staff, based on appropriate clinical criteria. The use of postoperative chemotherapy and/or radiation therapy for unresectable periampullary carcinoma was recommended to most patients and was employed selectively based on the recommendations of the surgeon, the referring physician, and the patient's preference.

Data Collection

Data were collected prospectively on all patients, including demographics, historical information, details about the surgical procedure, surgical findings, and clinical information regarding the postoperative course (both in-hospital and after discharge). Follow-up was completed through March 1999 on all patients, based on direct patient contact, hospital records, or the patient's family.

Data Analysis

The major endpoints for the study were short-term perioperative morbidity and mortality rates and late development of gastric outlet obstruction requiring intervention. Comparisons between the two groups were performed using analysis of variance, Student's t test, and chi square statistics. Determination of survival between the two groups was compared using the log-rank test. Results are reported as a mean $\pm$ SEM. Significance was accepted at the 5% level.

RESULTS

Patient Population

The study population consisted of 87 patients, with 44 patients receiving a retrocolic gastrojejunostomy and 43 patients not undergoing gastrojejunostomy. No significant differences in patient demographics, preoperative symptoms, or surgical findings were observed between the two groups, as shown in Table 1. The mean patient age was

Table 1. PATIENT DEMOGRAPHICS, PREOPERATIVE SYMPTOMS, AND SURGICAL FINDINGS

	Gastrojejunostomy (n = 44)	No Gastrojejunostomy (n = 43)
Age (yrs)	67 ± 1.5	67 ± 1.5
Gender		
Male	27 (61%)	23 (53%)
Female	17 (39%)	20 (47%)
Race		
White	38 (86%)	42 (97%)
Black	3 (7%)	1 (3%)
Other	3 (7%)	0 (0%)
Preoperative symptoms		
Jaundice	35 (80%)	30 (70%)
Weight loss	25 (57%)	24 (56%)
Abdominal pain	20 (45%)	22 (51%)
Nausea/vomiting	4 (9%)	3 (7%)
Tumor location		
Pancreas	42 (95%)	42 (98%)
Bile duct	1 (2%)	1 (2%)
Duodenum	1 (2%)	0 (0%)
Reason for unresectability		
Local invasion	25 (57%)	20 (47%)
Liver metastases	15 (34%)	20 (47%)
Peritoneal implants	4 (9%)	3 (7%)

67 ± 1.5 years in both groups. In the gastrojejunostomy group, 61% of the patients were men, compared with 53% in the no gastrojejunostomy group. The racial distribution was also similar: 86% of the patients in the gastrojejunostomy group and 97% of the patients not receiving a gastrojejunostomy were white. Obstructive jaundice was the most common presenting symptom; it was present in 80% of patients in the gastrojejunostomy group and 70% of patients in the no gastrojejunostomy group. Weight loss was present in 57% and 56% of the patients in the gastrojejunostomy and no gastrojejunostomy groups, respectively. Nausea and vomiting were present in 9% of the gastrojejunostomy patients and 7% of the patients not receiving a gastrojejunostomy. In all cases, gastroduodenal obstruction secondary to tumor was not presumed to be the cause of these symptoms.

Based on preoperative evaluation and surgical findings, the head of the pancreas was the predominant site of origin of the tumor. Ninety-five percent of patients receiving a gastrojejunostomy were thought to have tumors arising in the pancreas, compared with 98% of patients in the no gastrojejunostomy group. The most common reason for unresectability at the time of laparotomy was local major visceral vascular invasion: this was present in 57% of patients receiving a gastrojejunostomy and 47% of patients not receiving gastric bypass. Liver metastases were present in 34% of the gastrojejunostomy patients and 47% of the no gastrojejunostomy patients. Peritoneal implants were present in 9% and 7% of patients in the gastrojejunostomy and no gastrojejunostomy groups, respectively.

Table 2. SURGICAL MANAGEMENT

	Gastrojejunostomy (n = 44)	No Gastrojejunostomy (n = 43)
Hepaticojejunostomy	35 (80%)	36 (84%)
Chemical splanchnicectomy	39 (89%)	36 (84%)
Surgical time (min)	254 ± 9	209 ± 8*
Estimated blood loss (cc)	470 ± 100	332 ± 54
Transfusions (median)	0	0

* $p < 0.001$

The surgical management is listed in Table 2. A hepaticojejunostomy was performed in 35 patients (80%), and a chemical splanchnicectomy with 50% alcohol was performed in 39 patients (89%) undergoing gastrojejunostomy. A hepaticojejunostomy was performed in 84% of patients not receiving a gastrojejunostomy and a chemical splanchnicectomy in 84%. The total surgical time was 254 ± 9 minutes in the gastrojejunostomy group and 209 ± 8 minutes in the no gastrojejunostomy group ($p < 0.001$). The estimated blood loss and the median number of transfusions were not significantly different between the two groups.

Postoperative Complications and Length of Stay

Postoperative complications and length of stay are listed in Table 3. No postoperative hospital deaths or deaths within the first 30 days occurred after surgery. Fourteen

Table 3. POSTOPERATIVE FACTORS AND COMPLICATIONS

	Gastrojejunostomy (n = 44)	No Gastrojejunostomy (n = 43)
Perioperative deaths	0 (0%)	0 (0%)
Any complication	14 (32%)	14 (33%)
Cholangitis	4 (9%)	2 (5%)
Biliary anastomotic leak	3 (7%)	2 (5%)
Delayed gastric emptying	1 (2%)	1 (2%)
Wound infection	2 (5%)	0 (0%)
Pneumonia	1 (2%)	2 (5%)
Gastric anastomotic leak	0 (0%)	—
Postoperative hospital length of stay (days)	8.5 ± 0.5	8.0 ± 0.5

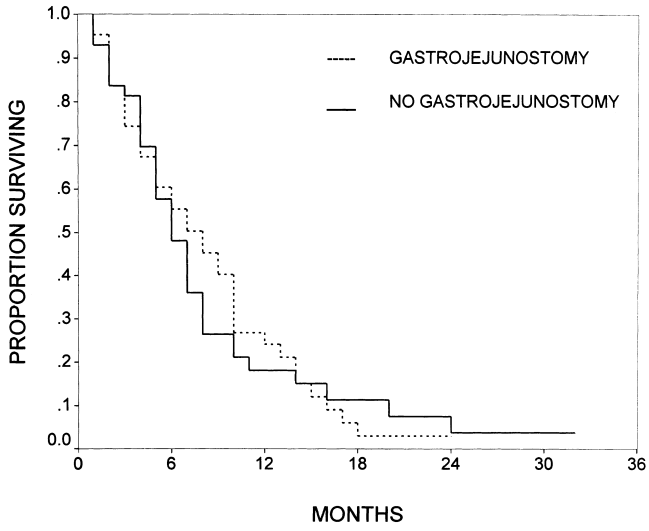

Figure 1. Actuarial survival curves for all patients with unresectable periampullary carcinoma undergoing gastrojejunostomy (n = 44) and no gastrojejunostomy (n = 43). The mean survival was 8.3 ± 0.9 months after gastrojejunostomy and 8.3 ± 1.2 months in patients not receiving a gastrojejunostomy (p NS).

patients (32%) undergoing a gastrojejunostomy had a postoperative complication. Similarly, 14 patients (33%) in the no gastrojejunostomy group had a complication. Postoperative cholangitis was the most common complication. Delayed gastric emptying occurred in 2% of patients in both groups. There were no cases of postoperative gastrojejunal anastomotic leak. There were five biliary anastomotic leaks; all closed spontaneously. The mean postoperative length of stay in the gastrojejunostomy group was 8.5 ± 0.5 days, which was not significantly different than the length of stay in the no gastrojejunostomy group (8.0 ± 0.5 days).

Long-Term Outcome and Survival

No statistical difference in survival was observed between the two groups (Fig. 1). The mean survival in the gastrojejunostomy group was 8.3 ± 0.9 months (median 8 months, range 1 to 24 months). In the no gastrojejunostomy group, the mean survival was 8.3 ± 1.2 months (median 6 months, range 1 to 32 months). Postoperative palliative chemotherapy with or without radiation was used in 38% of the patients who had undergone a gastrojejunostomy, whereas 44% of patients in the no gastrojejunostomy group received oncologic therapy.

In follow-up, late gastric outlet obstruction developed in none of the 44 patients undergoing a gastrojejunostomy. In 8 of the 43 (19%) not receiving gastrojejunostomy at the original procedure, late gastric outlet obstruction developed. The incidence of late gastric outlet obstruction in the no gastrojejunostomy group was significantly greater than in the gastrojejunostomy group ($p < 0.01$). A gastrojejunostomy was performed in seven of these patients. In one patient, a duodenal endostent was placed, and the patient's symptoms were palliated adequately.

The characteristics of patients undergoing late gastrojejunostomy are shown in Table 4. All patients had nausea and vomiting, with evidence of gastric outlet obstruction documented on endoscopy, upper gastrointestinal series, or computed tomography scan. The tumor location was the head of the pancreas in seven patients (87%), whereas in one patient, late gastric outlet obstruction developed with the primary tumor in the distal bile duct. Four patients (50%) had been considered to have unresectable disease as a result of local invasion, whereas three patients had liver metastasis (37%) and one patient had peritoneal implants (13%). The mean interval between the initial procedure and late gastrojejunostomy was 5.1 ± 2.3 months (range 1 to 16 months). There were no in-hospital deaths after late gastrojejunostomy, although one death occurred within 30 days of surgery (30-day mortality rate 12.5%). The mean survival (median 1 month) in patients undergoing "redo" gastrojejunostomy was 5.0 ± 1.8 months (range 0.3 to 16 months) after the secondary procedure, with an overall mean survival of 10.6 ± 3.4 months (range 2 to 32 months).

In addition to the patients who required an invasive procedure, late nausea and vomiting developed in three additional patients in the no gastrojejunostomy group (7%) but did not require hospital admission or intervention. Although four patients in the gastrojejunostomy group required hospital readmission (pain, Trousseau syndrome, biliary sepsis, benign bile duct stricture), significant nausea and vomiting did not develop in any patient before death.

DISCUSSION

The two options in the management of periampullary cancer are resection or palliation, depending on the stage of disease. In selected patients, pancreatic resection by pancre-

Table 4. CLINICAL CHARACTERISTICS OF EIGHT PATIENTS UNDERGOING LATE GASTROJEJUNOSTOMY

Tumor location	
Pancreas	7 (88%)
Distal common bile duct	1 (13%)
Tumor extent	
Local invasion	4 (50%)
Liver metastases	3 (38%)
Peritoneal implants	1 (13%)
Interval between initial operation and late gastrojejunostomy (mo)	
Mean	5.1 ± 2.3
Median	2
Range	1–16
Survival after late gastrojejunostomy (mo)	
Mean	5.0 ± 1.8
Range	0.3–16
Overall survival (mo)	
Mean	10.6 ± 3.4
Range	2–32

aticoduodenectomy offers a potential for cure. Many patients, however, have advanced disease at the time of presentation, precluding resection. Therefore, the goal in these patients is the palliation of symptoms. The primary symptoms of periampullary cancer include obstructive jaundice, duodenal obstruction, and pain. Currently, the palliation of obstructive jaundice by nonsurgical techniques is routine and is advocated in patients found to have unresectable disease by preoperative staging. The use of newer analgesic agents or the selective application of invasive techniques can control pain in most patients. Therefore, only the palliation of gastric outlet obstruction remains primarily in the realm of the surgeon. Recently, endoscopic palliation of duodenal obstruction using large-caliber metallic stents has been reported[12,13]; however, this experience has been limited, and long-term results are lacking.

At the time of diagnosis, 30% to 50% of patients note symptoms of nausea and vomiting.[6,14] Actual mechanical obstruction of the duodenum seen on radiographic or endoscopic examination at the time of presentation occurs less frequently. As unresectable disease progresses, however, duodenal obstruction occurs in a significant percentage of patients.

Three large reviews have assessed the role of prophylactic gastrojejunostomy in patients with unresectable periampullary cancer.[5–7] In a review by Sarr and Cameron of over 8000 surgically managed patients reported in the literature, 13% of patients who did not undergo gastric bypass at their initial surgical procedure required a gastrojejunostomy before death.[5] In addition, 20% of the remaining patients died with symptoms of duodenal obstruction. In a review of over 950 patients in the more recent literature by Singh et al,[6] the percentage who required a gastrojejunostomy at a later date was 21%. Finally, in a metanalysis review by Watanapa and Williamson[7] of over 1600 reported cases, duodenal obstruction requiring a gastric bypass developed at a mean of 8.6 months in 17% (range 4% to 44%) of patients who underwent biliary bypass alone. In none of these reviews did the performance of a gastrojejunostomy at the original surgical procedure increase the surgical mortality rate. However, in patients who required a second surgical procedure, mortality rates are generally high, approaching 25%. The authors of each of these collective reviews advocated routine prophylactic gastrojejunostomy in patients undergoing laparotomy for unresectable pancreatic cancer.

These data from surgical series have also been confirmed in patients with unresectable pancreatic cancer undergoing nonsurgical palliation. Prospective, randomized trials of nonsurgical *versus* surgical palliation for malignant biliary obstruction have also demonstrated a significant incidence of late gastric outlet obstruction.[8–10] In three series in which endoscopic stenting was compared with surgical palliation, including combined biliary and gastric bypass, the incidence of late gastric outlet obstruction ranged from 9% to 14% in the nonsurgical arms. The performance of a gastrojejunostomy at the time of surgical palliation decreased the incidence of late gastric outlet obstruction to 0% to 4%.

Despite the results of these collective reviews and the prospective trials of nonsurgical management, significant controversy continues concerning the role of prophylactic gastrojejunostomy. A number of series have shown an increase in postoperative morbidity rates, primarily delayed gastric emptying, with this procedure. Doberneck and Berndt[15] reported an overall mortality rate of 18% and an incidence of postoperative delayed gastric emptying of 26%. The mortality rate in patients with delayed gastric emptying was 33%. Similarly, the group at Wayne State University reported an unfavorable short-term outcome, ranging from a 40% incidence of complications in patients with no evidence of duodenal obstruction to 90% in patients with preoperative nausea and vomiting.[16] Citing these excessive perioperative morbidity and mortality rates, Lucas et al[17,18] have advocated antrectomy with Billroth II reconstruction rather than gastrojejunostomy as the procedure of choice in the setting of duodenal obstruction.

Other authors have suggested that the limited long-term survival in patients with unresectable periampullary cancer eliminates the need for prophylactic gastrojejunostomy. In a retrospective series reported by Egrari and O'Connell,[19] 50 patients with unresectable pancreatic cancer underwent biliary decompression without prophylactic gastrojejunostomy. Duodenal obstruction developed in only 4 of the 50 patients (8%); they required reoperation for therapeutic gastrojejunostomy. The mean time to developing obstruction was 15.8 months, whereas the mean overall survival was 13.0 months. These authors suggested that with the often rapid natural progression of unresectable pancreatic cancer, most patients do not survive long enough to have an obstruction. They concluded that prophylactic gastrojejunostomy was unnecessary. Similarly, in a series from Memorial Sloan-Kettering, the addition of a prophylactic gastrojejunostomy was associated with a significant increase in the perioperative morbidity rate.[20] Furthermore, the occurrence of delayed gastric emptying in that series was associated with a significantly increased perioperative morbidity rate. These authors also concluded that the overall poor prognosis with unresectable pancreatic cancer does not warrant prophylactic gastric bypass.

Furthermore, the role for gastrojejunostomy in unresectable periampullary cancer has been questioned by those who advocate routine laparoscopic staging for pancreatic cancer. In a recent series from Memorial Sloan-Kettering, 155 patients were found to have unresectable adenocarcinoma of the pancreas at the time of laparoscopic staging.[21] None progressed to an open exploration, and in no case was a gastrojejunostomy performed at the time of initial management. Only three patients (2%) required a subsequent gastrojejunostomy. These results are notable in that 25% of patients had nausea and 12% reported emesis at the time of presentation. The authors concluded that laparoscopic stag-

ing can avoid laparotomy in many patients and that prophylactic gastrojejunostomy cannot be supported.

The palliation of unresectable periampullary cancer at Johns Hopkins for the past 20 years has included prophylactic gastrojejunostomy. The gastrojejunostomy, however, is routinely performed in a retrocolic, dependent position. Many groups have avoided the retrocolic anastomosis in favor of an antecolic position, attempting to avoid placement of the anastomosis near the tumor. We have found that performing the gastrojejunostomy in a retrocolic fashion, rather than antecolic, virtually eliminates the problems of postoperative delayed gastric emptying. Two series from our institution describing our experience with surgical palliation of pancreatic cancer have demonstrated the effectiveness of the retrocolic technique. In the first report, the overall incidence of postoperative delayed gastric emptying was 8%.[14] In that series, postoperative delayed gastric emptying developed in only 5 of 84 patients (6%) undergoing a retrocolic gastrojejunostomy, *versus* 4 of 23 patients (17%) with the anastomosis in the antecolic position ($p = 0.08$). In follow-up, late obstruction developed in only 2 of 84 patients (2%) with a retrocolic gastrojejunostomy, *versus* 9% in the antecolic group ($p = 0.16$). In the most recent series,[4] including the time period of the current study, a retrocolic gastrojejunostomy was performed in 180 patients. The incidence of delayed gastric emptying was 9%, with a postoperative length of stay of 10.1 ± 0.3 days. In long-term follow-up, recurrent duodenal obstruction developed in only 2% of patients before death.

Despite the abundance of studies, this current series represents the first prospective, randomized trial of gastrojejunostomy performed for unresectable periampullary carcinoma. The results of this study appear to support the role for prophylactic gastrojejunostomy in patients undergoing laparotomy for unresectable periampullary carcinoma. The randomization appeared to generate comparable groups in that there were no significant differences in patient demographics, preoperative symptoms, or surgical findings. The surgical procedures performed, with the exception of gastrojejunostomy, were similar in both groups. The extent of disease was also similar in the two groups, with major visceral vessel invasion precluding resection in 57% of the gastrojejunostomy group and 47% of the control group. The only significant difference related to the groups, with respect to perioperative results, was the surgical time: as expected, the performance of a prophylactic gastrojejunostomy added a mean of 45 minutes. Estimated blood loss and the median number of transfusions, however, were not different between the two groups. Furthermore, there were no differences in perioperative morbidity or mortality rates or length of stay. Postoperative delayed gastric emptying occurred in 2% of patients in both groups. There were no cases of postoperative gastrojejunal anastomotic leak.

The benefits of prophylactic gastrojejunostomy were demonstrated in a long-term follow-up. Survival in the two groups was similar: 8.3 ± 0.9 months in the gastrojejunostomy group and 8.3 ± 1.2 months in the control group. However, patients not undergoing a gastrojejunostomy had a marked and highly significant increase in the need for late intervention for gastric outlet obstruction. Late gastric outlet obstruction symptoms, requiring intervention, developed in 8 of 43 patients (19%) not receiving a gastrojejunostomy at the original procedure. A gastrojejunostomy was performed in seven of these patients, with one patient successfully managed with a duodenal endostent. The mean interval between the initial surgical procedure and late intervention was 5.1 ± 2.3 months (range 40 days to 16 months). One patient died within 30 days of the performance of the gastrojejunostomy; however, the mean survival after late gastrojejunostomy was 5.0 ± 1.8 months. The need for intervention for late gastric outlet obstruction was equally divided between patients considered to have unresectable disease as a result of local invasion and those with disseminated disease, suggesting that extent of disease cannot be used to predict late obstruction.

This study was strengthened in that patients were included in the randomization only if their attending surgeon believed that gastric outlet obstruction was not likely based on preoperative symptoms, radiologic studies, or surgical findings. The fact that only 87 of 194 patients (45%) thought to have unresectable disease were included in the randomization demonstrates that great care was taken to exclude any patient in whom the surgeon believed duodenal obstruction could possibly develop. Despite that selection, 19% of the patients not undergoing a prophylactic gastrojejunostomy became obstructed and required treatment.

In conclusion, this single-institution, prospective, randomized trial strongly supports the prophylactic use of gastrojejunostomy in patients with periampullary cancer found to have unresectable disease at laparotomy for possible pancreaticoduodenectomy. The addition of a prophylactic gastrojejunostomy, although adding to surgical time, does not significantly increase perioperative morbidity or mortality rates or length of hospital stay. The incidence of late gastric outlet obstruction in this selected group of patients not undergoing gastrojejunostomy was 19%, which is consistent with previous retrospective series. A retrocolic gastrojejunostomy should be performed routinely when a patient is undergoing surgical palliation for unresectable periampullary carcinoma.

Acknowledgments

The authors thank Donna Greul for her excellent technical support in preparation of the manuscript and the surgical house staff and nurses of The Johns Hopkins Hospital, without whose dedication and skill this study would not have been possible.

References

1. Trede M. The surgical treatment of pancreatic carcinoma. Surgery 1985; 97:28–35.

2. Singh SM, Longmire WP, Reber HA. Surgical palliation for pancreatic cancer. Ann Surg 1990; 212:132–139.
3. Warshaw AL, Gu Z, Wittenburg J, et al. Preoperative staging and assessment of resectability of pancreatic cancer. Arch Surg 1990; 125:230–233.
4. Sohn TA, Lillemoe KD, Cameron JL, et al. Surgical palliation of unresectable periampullary adenocarcinoma in the 1990s. J Am Coll Surg 1999; 188:658–669.
5. Sarr MG, Cameron JL. Surgical management of unresectable carcinoma of the pancreas. Surgery 1982; 91:123–133.
6. Singh SM, Longmire WP, Reber HA. Surgical palliation for pancreatic cancer. Surg Clin North Am 1989; 69:599–611.
7. Watanapa P, Williamson RCN. Surgical palliation for pancreatic cancer: developments during the past two decades. Br J Surg 1992; 79:8–20.
8. Bornman PC, Harries-Jones EP, Tobias R, et al. Prospective controlled trial of transhepatic biliary endoprosthesis *versus* biliary bypass surgery for incurable carcinoma of the head of the pancreas. Lancet 1986; 1(8472):69–71.
9. Dowsett JF, Russell RCG, Hatfield ARW, et al. Malignant obstructive jaundice: a prospective randomized trial of bypass surgery *versus* endoscopic stenting. Gastroenterology 1989; 96:128A.
10. Shepard HA, Royle G, Ross APR, et al. Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: a randomized trial. Br J Surg 1988; 75:1166–1168.
11. Lillemoe KD, Cameron JL, Kaufman HS, et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer: a prospective randomized trial. Ann Surg 1993; 217:447–457.
12. Lichtenstein, DR, Carr-Locke DL. Endoscopic palliation for unresectable pancreatic carcinoma. Surg Clin North Am 1995; 75:969–988.
13. Maetani I, Ogawa S, Hoshi H. et al. Self-expanding metal stents for palliative treatment of malignant biliary and duodenal stenoses. Endoscopy 1994; 26:701–704.
14. Lillemoe KD, Sauter PK, Pitt HA, et al. Current status of surgical palliation of periampullary carcinoma. Surg Gynecol Obstet 1993; 176:1–10.
15. Doberneck RC, Berndt GA. Delayed gastric emptying after palliative gastrojejunostomy for carcinoma of the pancreas. Arch Surg 1987; 122:827–829.
16. Weaver DW, Wiencek RG, Bouwman DL, et al. Gastrojejunostomy: is it helpful for patients with pancreatic cancer? Surgery 1987; 102:608–613.
17. Lucas CE, Ledgerwood AM, Bender JS. Antrectomy with gastrojejunostomy for unresectable pancreatic cancer causing duodenal obstruction. Surgery 1991; 110:583–590.
18. Lucas CE, Ledgerwood AM, Saxe JM, et al. Antrectomy: a safe and effective bypass for unresectable pancreatic cancer. Arch Surg 1994; 129:795–798.
19. Egrari S, O'Connell TX. Role of prophylactic gastroenterostomy for unresectable pancreatic carcinoma. Am Surg 1995; 61:862–864.
20. Rooij PD, Rogatko A, Brennan MF. Evaluation of palliative surgical procedures in unresectable pancreatic cancer. Br J Surg 1991; 78: 1053–1058.
21. Espat NJ, Brennan MF, Conlon KC. Patients with laparoscopically staged unresectable pancreatic adenocarcinoma do not require subsequent surgical biliary or gastric bypass. J Am Coll Surg 1999; 188: 649–657.

Discussion

DR. MICHAEL G. SARR (Rochester, Minnesota): I hope this paper will be the definitive study on this topic from my old alma mater. Many people in the audience, especially upper gut surgeons, have their own experience based on treatment of these patients, what outcomes they have experienced, and what they have interpreted from review of the literature.

About 20 years ago, Dr. Cameron and I compiled a collected series from the literature of over 8,000 patients with unresectable pancreatic cancer to answer this time-old question. We came up with the same incidence of postoperative gastric outlet obstruction in patients who did not undergo a gastroenterostomy, and I think Dr. Cameron and I at that time would have thought the question had been answered. This stimulated a study by myself and my colleagues at the Mayo Clinic on this same topic and found similar incidence. What we don't know, Dr. Lillemoe, is what is the incidence of gastric outlet obstruction during follow-up from a symptomatic standpoint in these patients that aren't reoperated on?

But I am sure there are going to be some skeptics in the audience, because most of us feel that if you do a gastroenterostomy, there is somewhat of an increase in delay to discharge. Also, the patients in our later study who did develop delayed gastric emptying postoperatively were largely those with some signs of obstruction preoperatively.

I have two questions. First, in those 107 patients in whom a gastroenterostomy was done specifically because the surgeon thought that there was a chance of impending duodenal obstruction, what was the hospitalization duration of those patients? I would have postulated they did have a somewhat increased incidence of delayed gastric emptying. Second, as with your previous study for pancreatectomies, what type of pharmacologic prokinetic protocol do you use in these patients?

PRESENTER DR. KEITH D. LILLEMOE (Baltimore, Maryland): In answer to your first question, at last fall's American College of Surgeons, we presented our experience in surgical palliation of unresectable periampullary carcinoma. In that series, we included the randomized patients that were presented as well as those patients who received a gastrojejunostomy based on clinical indications. This series also included those patients who were operated on specifically for symptoms of gastric outlet obstruction. In that series, the incidence of postoperative delayed gastric emptying was 9% and the mean length of stay was 10.1 days.

In answer to your question about the use of prokinetic agents, as you know, Charles Yeo of our group several years ago at this Association presented a prospective randomized trial investigating the use of erythromycin to prevent delayed gastric emptying after pancreaticoduodenectomy, and showed some advantages of that treatment. At our institution, I think intravenous metoclopramide now tends to be the drug of choice in those patients in which delayed gastric emptying occurs either after a Whipple procedure or a palliative procedure. When patients are discharged, they are either switched over to oral metoclopramide or cisapride. These agents are not used routinely, but if there is any suggestion that problems might be developing, they are used frequently.

DR. CHARLES E. LUCAS (Detroit, Michigan): It gives me great pleasure to discuss this manuscript, which I hope will *not* be the definitive paper on this topic.

Wosler in 1881 performed the first palliative gastrojejunostomy for malignant gastric outlet obstruction and by 1883 developed the "anastomosis-en-Y" to prevent "bilious vomiting." Most of Cesar Roux's 50 references in his classic 1897 paper dealt with the dysfunction of gastrojejunostomy. Although Mikulicz in 1903 reported less dysfunction with a retrocolic anastomosis, hundreds of authors have reported dismal results, including Pribram, who stated in 1923, "gastrojejunostomy is a disease and not an operation," and today's authors, who reported in 1993 a 17% and 6%

incidence of delayed gastric emptying after the antecolic and retrocolic anastomosis, respectively. My first question, therefore, is: What are you doing differently to reverse more than a century of frustration?

Alec Walt in 1987 reported that this operation never works in those who really need relief and only gives the illusion of functioning in those who don't need relief. Barium studies performed prior to discharge and at the time of readmission for impending outlet obstruction showed preferential emptying through the narrow duodenum and gastric refilling through the gastrojejunostomy. My second question, therefore, is: Do you have radiographic confirmation of your proposed benefits of this operation?

Based on Alec Walt's report, I initiated palliative antrectomy with antecolic reconstruction in 1987. Currently, our series exceeds 80 patients. None have developed outlet obstruction, and I sincerely believe they live longer because they are free of "bilious vomiting."

Thus, my challenge to the authors is to prospectively compare antrectomy with antecolic anastomosis to the retrocolic gastrojejunostomy and report to this body in the year 2003, 100 years after Mikulicz's report on the efficacy of the retrocolic gastrojejunostomy, that this operation is superior to palliative antrectomy.

DR. LILLEMOE: Dr. Lucas brings up a somewhat controversial point with respect to the performance of a gastrojejunostomy—that is, whether it should be performed antecolic or retrocolic. For generations, surgeons were taught that the antecolic position was preferable because it avoids placing the gastrojejunostomy in the so-called bed of the tumor.

He referred to a paper that we published in 1993. In that study, which was not prospective nor randomized, we reported over 100 patients who had a gastrojejunostomy at our institution, some of which had been done in an antecolic fashion, but most retrocolic. In a nonrandomized comparison, the incidence of delayed gastric emptying in the antecolic group was 17%, whereas in the patients who had a retrocolic gastrojejunostomy it was only 6%. In follow-up, only 2% of patients with a retrocolic gastrojejunostomy developed late obstruction *versus* 9% in the antecolic group. These data suggested that a retrocolic anastomosis has both a decreased incidence of postoperative delayed gastric emptying, but also was not at a higher risk for late obstruction. We are very careful technically in the performance of a gastrojejunostomy. We generally perform it in the dependent distal position, in an isoperistaltic manner. We choose a site on the jejunum distal to the ligament of Treitz so that the loop lays comfortably. After the anastomosis is completed, we pull the jejunum back down through the defect in the mesocolon and tack it at that point. I think if one takes a lot of care in performing this procedure, you can decrease the incidence of complications.

We do not routinely perform radiographic evaluation prior to the hospital discharge or in follow-up. If patients do present with late symptoms, they are evaluated either with barium studies or endoscopy.

Finally, I am well aware of your work with respect to antrectomy. Your results in palliation of duodenal obstruction are excellent and in selected patients an antrectomy might be appropriate. However, I feel that in unresectable patients with limited life expectancy, that adding a prophylactic gastric resection to an operation that I know some people in the audience probably feel is already unnecessary, seems a little bit too aggressive.

DR. CLARENCE DENNIS (Mendota Heights, Minnesota): It is a source of pride to Dr. Richard Varco and me that the authors have seen fit to deal with this problem, since apparently we were first to report that duodenal obstruction is a lethal complication of cancers of the ampulla and pancreatic head.

Insofar as we know, ours was also the first suggestion that gastroenterostomy should be a part of any exploration for cancer of the ampulla or of the pancreatic head which shows that lesion not to be resectable with intent to cure.

This appeared in *Surgery*, volume 20, number 1, on page 72 in 1946. The recommendation for GE is on page 79. Our suggestion was a rather tentative one, and yet gastroenterostomy was regularly employed by both of us from that point on as part of any operation for cancer of ampulla, pancreatic head, or lower common duct in which the lesion was found not to be resectable with cure in mind.

The authors of the superlative paper we have just heard are to my knowledge the first to acquire sufficient numbers to perform such a study. They have confirmed in a solid statistical study that this is the proper course to follow. This group of surgeons has fulfilled our fondest dreams with its outstanding record of accomplishment in this field. It makes me prouder than ever that the Johns Hopkins Medical School is my alma mater.

DR. LILLEMOE: Thank you, sir. Your contribution and the contribution of many others in the audience with this disease has certainly brought this question to bear. I do think that finally, though, after all of these years, a prospective randomized trial was long overdue and it is our pleasure to report it today to this group.

DR. ANDREW L. WARSHAW (Boston, Massachusetts): Dr. Lillemoe, this is another in a series of really terrific trials trying to get rid of prejudice and get the facts. I do have a problem because your facts seem to contradict my biases. We have not to date done prophylactic gastrojejunostomies. On the basis of my unpublished, undocumented, unproven observations, I will go out on a limb and say we very rarely see late gastrojejunal obstructions.

So why the difference between your perceptions and mine? It is clear that you have not added to length of life, but I accept the fact that you appear to have added to quality of life and reduced costs by eliminating a second operation.

My problem, in looking at your data, is in the selection of patients, and maybe that is where we differ. You comment in your manuscript that only 75% of the patients who were randomized in this series had obstructive jaundice. Why do you call this a periampullary cancer if the patients don't have obstructive jaundice? Could your selection of nonjaundiced patients explain bias toward late duodenal obstruction?

My interpretation is that you are including a number of patients who have uncinate process tumors that are distal to the ampulla and which would have a high risk of late obstruction because of their location related to the duodenal sweep, especially at the third and fourth portions. In contrast, a cancer of the upper pancreatic head or a bile duct tumor might be less likely to impinge on the duodenal lumen. Therefore, my question is: What are the criteria that your surgeons used for inferring that a patient didn't have impending obstruction? Those criteria might define the difference between our experiences and perhaps define subgroups that really do need a gastrojejunostomy.

I would also ask whether your observations change your approach to choosing patients for operation? If you believe that prophylactic gastrojejunostomy is an important component of

treatment for patients with periampullary cancers, should we stop doing nonoperative biliary stenting and operate on all patients in order to do the prophylactic gastrojejunostomy?

DR. LILLEMOE: With respect to whether you see a problem with late gastric outlet obstruction or not really depends on how hard you look for it. Your group in Boston, Dr. Brennan at Memorial, and certainly we at Hopkins have national and sometimes international referral patterns. Therefore, unless you really prospectively follow these patients, call them when they return back to their homes halfway across the United States to find out whether they are having problems, you may be missing late problems. Three of our eight patients actually had their follow-up procedures performed at outside hospitals, not at Johns Hopkins. So if we had not prospectively followed these patients, their long-term outcome may have been unknown.

With respect to the fact that about 75% of our patients were not jaundiced, when we look at our percentage of our patients undergoing Whipple procedure, or those reported in our recent series of surgical palliation, only about 75% of patients are jaundiced. It is likely that many of these tumors do arise in the uncinate process. This is also an area which will frequently be unresectable due to local visceral vessel invasion. You probably are right that uncinate tumors have a higher propensity to cause obstruction than an ampullary, distal bile duct or head of the pancreas tumor. When we looked at those patients in our series who were not jaundiced and did not receive a gastrojejunostomy, however, none of these patients developed late duodenal obstruction. With respect to what factors lead us to decide whether to include or not to include a patient in the randomization, it really varies from surgeon to surgeon. There were four surgeons who contributed most of these patients, and we each had a different threshold for entering a patient into the randomization process. Certainly, persistent symptoms of nausea and vomiting, or endoscopic exams, upper GI series, or CT scans that demonstrated near-complete obstruction were “no-brainers.” But at operation it is sometimes hard to tell. I think this series, with relative conservative inclusion of patients into the randomization process, would suggest that we cannot really predict who is going to have a problem with late obstruction.

Your final question really is challenging. And again for those of you in the audience—yourself, Dr. Brennan—who favor laparoscopic staging of these patients, I think that technique could also be included. As you know, our institution does not routinely laparoscopically stage patients with periampullary cancer. We feel that at the time of laparotomy we can do a very thorough exploration and attempt to resect as high a percentage of patients as we possibly can. But in patients found to be unresectable, we feel that with the performance of hepaticojejunostomy, a retrocolic gastrojejunostomy, and a chemical splanchnicectomy, we can eliminate just about all symptoms that could bother that patient between their operation and their death.

I don’t believe, however, the data would suggest that a patient who presents with widespread metastases or carcinomatosis should undergo laparotomy simply to perform a gastrojejunostomy.